THE X-RAY TREATMENT OF STATUS LYMPHATICUS, WITH INFERENCES DRAWN THEREFROM CONCERNING THE PHYSIOLOGY OF THE THYMUS GLAND.[1]

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In 1907 Alfred Friedlander[2] reported a case of status lymphaticus with marked enlargement of the thymus and persistent stridor, which he treated successfully by the *x*-rays. Heinecke (quoted by Friedlander) demonstrated the selective action of the Röntgen rays on lymphoid tissues, including the thymus, and showed that under their action marked changes occurred in these tissues, with a reduction in their size. Friedlander's successful case directed attention to the *x*-ray treatment of enlarged thymus in connection with status lymphaticus, and led to the successful treatment by this method of a number of other cases. The purpose of this paper is to call attention to two of these cases which came under my direct observation, and to draw therefrom certain inferences concerning the physiology of the thymus gland.[3]

Case I.—John X., born July 2, 1908, birth weight 6½ pounds, was apparently normal for one month, and was then weaned because of indigestion. When one month of age he choked on a calomel and soda powder, became greatly cyanosed, and was prostrated for a number of hours afterward. From this time on his mother noticed that there was great difficulty in keeping his feet warm, and that at times they were blue. About the middle of December, when five and one-half months old, he had an afebrile attack of "bronchitis" of the larger tubes, characterized by cough, coarse rales, wheezing, and dyspnœa; this attack lasted one month. In the middle of February he developed another attack of bronchitis, with the same symptoms as in the preceding attack, except that the cough was more violent and spasmodic. This attack continued until, on March 4, his adenoids were removed under chloroform anesthesia, in the hope of relieving these symptoms. Following the operation the child was better for two days, when the whole symptom group recurred; at this time there was marked stridor and dyspnœa, which interfered with his taking food. On April 3 a second and more radical operation was made for the removal of the adenoids and tonsils. Following this operation for two or three days there was a slight improvement in his symptoms, and then his condition grew steadily worse. The cyanosis, stridor, and prostration increased until on April 12 he was brought to Cincinnati with the diagnosis of thymic asthma. I saw him on his arrival, and asked Drs. Forchheimer and Friedlander to see the case with me. We concurred in the opinion that the child had status lymphaticus and was suffering from thymic asthma, The thymus gland, greatly enlarged, was readily mapped out by percussion. A blood examination by Friedlander showed a chloro-anemia and a well-marked lymphocytosis. The patient was pale, fat, and flabby. He suffered constantly from stridor, so severe that it was almost impossible for him to take food. He also had a severe paroxysmal cough, which came on at short intervals and increased the stridor into an attack of asthma associated with such great cyanosis that his life was threatened. The child was held the greater portion of the time stomach down, across the mother's lap; in this position the stridor was less severe. The lymphatic glands were increased in size, the spleen was slightly enlarged, and, as previously noted, the adenoids and tonsils had been removed. The tuberculin skin test was negative.

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[1] Read by title at a meeting of the Association of American Physicians, Washington, D. C., May 4, 1910.

[2] Archives of Pediatrics, July, 1907.

[3] For many of the facts used in this paper I am indebted to the writings of A. S. Warthin, in Osler's System of Medicine, the Transactions of the Association of American Physicians, 1906, and the Archives of Pediatrics, August, 1909; and to Pappenheimer's paper on the Histology of the Thymus Gland, in the Journal of Medical Research, February, 1910.

So urgent were the symptoms that the *x*-ray treatment was begun on the day of his arrival in Cincinnati, April 12, 1909. At each treatment the rays were applied both anteriorly and posteriorly over the region of the thymus. The rest of the body was carefully guarded from their influence. Sixteen treatments in all were given, extending over a period of six weeks. In the beginning the time of exposure to the rays was three minutes anteriorly and three minutes posteriorly. In the later treatments the exposure was eight minutes. The treatment was interrupted during the fourth week.

Within forty-eight hours after beginning the treatment there was slight improvement in the symptoms, especially the stridor, and this improvement continued steadily throughout the eight weeks he was under treatment. During this time the thymus gland was reduced to its normal size, and the dulness posteriorly on the left under the angle of the scapula, which we thought to be due to lymphatic enlargement and pulmonary compression, also disappeared. The paroxysmal cough and stridor had been almost entirely relieved and the child had gained steadily in weight and strength, but he still appeared anemic. On May 17 he was taken to his home in Kentucky, and within two weeks thereafter his father, who is a physician, reported that the cough and stridor had entirely disappeared, and that the child was apparently well. From the time the child returned home until the present time, April 11, 1910, he has had, at intervals of about three months, three very slight attacks characterized by cough and dyspnœa, which occurred without apparent cause and which were promptly relieved by one or two mild *x*-ray treatments. Apart from this he has presented the appearance of a sturdy infant developing along normal lines. His father wrote me on April 11: "It will be just one year ago tomorrow since I took my baby to see you, and he now seems to be perfectly well. About three months ago he had another slight recurrence, which yielded promptly to two mild exposures to the *x*-rays. It seems that he may from time to time need an occasional treatment, but I shall remember your advice and not expose him to the rays unless there seems real occasion for it."

CASE II.—John Y., born July, 1908. When about six months of age it was noted that he had rapid heart action and difficulty in breathing from slight causes. From this time on these symptoms gradually increased in severity and the general symptom complex of status lymphaticus slowly became apparent. On November 1, 1909, I saw the patient for the first time with Dr. Sam Rothenberg, and from this time on he was cared for jointly by Dr. Rothenberg and myself. On this date the child was fifteen and one-half months old and presented well-marked and aggravated symptoms of status lymphaticus, which Dr. Rothenberg informed me had existed for some months. He was fat, flabby, anemic, and markedly lacking in physical development, especially his lower extremities. He had great dyspnœa, with well-marked stridor, which at times during the last few months was greatly aggravated by such slight causes as fits of anger, indigestion, and catarrhal conditions of the throat and nose. The child at times had a spasmodic cough, which would aggravate the stridor and produce cyanosis. The heart was dilated and its muscle weak and irritable. The action of the heart was rapid at all times, and this rapidity was greatly increased by the same causes which aggravated the stridor. The spleen, lymph nodes, and tonsils were enlarged, and there was a marked itching of the skin of the face and head, which caused the child to mutilate the skin of these regions by scratching. A well-marked enlargement of the thymus was demonstrated by percussion, and a blood examination by Dr. Max Dreyfoos demonstrated a very pronounced chloro-anemia and well-marked lymphocytosis. The blood examination was as follows: Hemoglobin, 65 to 70 per cent.; red corpuscles, fresh preparation, showed considerable poikilocytosis, a few "ameboid" micropoikilocytes, and, on the whole, the red cells were smaller than normal; the stained preparation showed 6 normoblasts to 500 whites counted; white corpuscles, 24,600; red corpuscles, 5,881,250; color index, 0.58; differential count, polymorphonuclear neutrophiles, 25.6 per cent. small lymphocytes, 61.8 per cent.; large lymphocytes, 2.6 per cent.; large mononuclear leukocytes, 8.4 per cent.; eosinophiles, 0.6 per cent.; mast cells, 1 per cent.

The patient was immediately referred to Dr. Sidney Lang for *x*-ray treatment. In all, twelve treatments were given during the next six weeks, and during this time the symptoms of status lymphaticus gradually improved. There was an early and marked diminution in the size of the thymus and marked improvement in the stridor and heart action; the spleen and lymph nodes grew smaller and the itching of the skin largely disappeared, but the child still presented a very anemic appearance. A blood examination on December 26, 1909, showed that the lymphocytosis had disappeared, but that the chloro-anemia was slightly more aggravated than before. The blood state at this time was as follows: Hemoglobin, 50 to 55 per cent.; fresh preparation, reds pale and smaller than normal; considerable poikilocytosis and anisocytosis; stained preparation, polychromatophilia; 2 nucleated reds to 300 whites counted; white corpuscles, 6,800; red corpuscles, 4,675,000; color index, 0.56; differential count, polymorphonuclears, 38 per cent.; small lymphocytes, 46 per cent.; large lymphocytes, 6 per cent.; large mononuclear leukocytes, 7.67 per cent.; eosinophiles 1.66 per cent.; mast cells 0.67 per cent.

Following the above blood examination the *x*-ray treatment was discontinued and the child was given citrate of iron hypodermically. He continued to improve in general health and the slight amount of dyspnœa which still appeared at times continued to grow less. The heart was gradually reduced in size and its action became more normal. This improvement continued until January 12, when the child was taken ill with bronchopneumonia, from which he made a rapid recovery. February 27, a blood examination was made, with the following results: Hemoglobin, 90 per cent.; fresh preparation, reds smaller than normal; moderate poikilocytosis; considerable anisocytosis; rouleaux formation fairly well marked; white corpuscles, 14,500; red corpuscles, 5,906,250; differential count, polymorphonuclears, 69.25 per cent.; small lymphocytes, 22.5 per cent.; large lymphocytes, 3.25 per cent.; large mononuclears, 3.25 per cent.; eosinophiles, 1.5 per cent.; mast cells, 0.25 per cent.

It will be noted that the special point of interest in the above blood picture is the appearance of a polymorphonuclear leukocytosis, while the lymphocyte count remains low. It was suggested by Dr. Dreyfoos that this might be due to a slight influenza which the baby had at the time, and which had developed after Dr. Rothenberg and I had seen the baby and asked for the blood count on February 20. In this connection, however, it may be interesting to note that Rudberg, quoted by Pappenheimer, notes in his study of the regeneration of the thymus in rabbits following Röntgenization, that during the later stages of this regeneration there is a marked invasion of the thymus gland with polynuclear leukocytes derived from the blood. This would indicate that a polynuclear leukocytosis might be a physiological reaction following the *x*-ray treatment of the thymus. Without other treatment than fresh air and careful feeding this child continued to improve in general health, until on April 5, 1910, he presented the appearance of a normal child. The dilated heart had returned almost to normal size, and none of the symptoms of status lymphaticus were present. The child at this time was gaining in weight and developing along normal lines, and the blood state below given is almost, if not quite, normal: Hemoglobin, 75 to 80 per cent.; fresh preparation, red corpuscles slightly under normal size; small number of poikilocytes; white corpuscles, 9800; red corpuscles, 4,881,250; color index, 0.9; differential count, polymorphonuclears, 48.33 per cent.; small lymphocytes, 39.67 per cent.; large lymphocytes, 2.66 per cent.; large mononuclear leukocytes, 3.67 per cent.; eosinophiles, 5.33 per cent.; mast cells, 0.34 per cent.

A study of this case indicates that the disappearance of the lymphocytosis under the *x*-ray treatment of the thymus gland in status lymphaticus is so marked that a careful study of the blood state in this condition will give important information not only as to the efficacy of the treatment, but as to the length of time this treatment should be continued. It will perhaps be wise to discontinue treatment when the lymphocytosis disappears, even though there still be left some cough and stridor. The chloro-anemia which is not improved under the *x*-ray treatment may be aggravated if it be continued too long. Following the *x*-ray treatment in these cases, hypodermic injections of iron, with careful feeding and fresh air, may be necessary to restore the blood state to a normal condition. In both of the cases here reported slight cough and stridor were present when the *x*-ray treatments were discontinued, but disappeared entirely a few weeks later.

PHYSIOLOGY OF THE THYMUS. The histology of the thymus gland is very fully discussed by Pappenheimer.[4] It appears that while many points concerning the development and histology of this gland are still in dispute, it is rather generally conceded that it is relatively large in infancy and early childhood, but that it gradually increases in size up to the fifteenth year of life, and thereafter regressive changes slowly take place which diminish its physiological efficacy. It is also very generally believed that the thymus furnishes an internal secretion which exerts an important influence on nutritional processes, and that its period of greatest functional activity along this line is during fœtal life and early childhood; this function falls off most rapidly after the fifteenth year, but probably remains more or less active throughout life. For a review of the various inferences and suggestions which have been made concerning the physiological functions of this gland the reader is referred to the papers by Warthin, previously noted.

It is my purpose here to call attention to the following facts, which I believe have been demonstrated by the *x*-ray treatment of the enlarged thymus gland in the condition known as status lymphaticus, and based upon these facts I shall offer an hypothesis concerning the functions of this gland, which, if true, will have an important bearing upon the pathology of this disease.

In the *x*-ray treatment of status lymphaticus in infants and young children, although no portion of the body is exposed to the influence of the rays except that which directly holds the thymus gland, we have as a result of this treatment:

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[4] Journal of Medical Research, February, 1910.

1. Decrease in size of the hyperplastic thymus, with the disappearance of the cough, stridor, and asthma.
2. Decrease in size of the enlarged spleen and lymph nodes.
3. The exhaustion and general feebleness of constitution gives place to normal conditions of health and strength, and physical and intellectual growth are greatly stimulated.
4. A rapid disappearance of the marked lymphocytosis which characterizes this disease.
5. Excessive physiological action of the thymus gland is controlled. The slight return of the symptoms, stridor, cough, etc., at intervals of three or four months in one of my cases, and the quick control of these symptoms by one or two exposures to the *x*-rays, indicate that the gradual regeneration of the thymus following the *x*-ray treatment may be accompanied by a gradual reproduction of the same pathological conditions, hypersecretion, etc., which were present before the treatment was begun.

Since the above remarkable results are brought about by the action of the *x*-rays on the thymus gland, it would appear that the excessive physiological activity of the thymus gland bears the same relationship to status lymphaticus that excessive activity of the thyroid gland bears to exophthalmic goitre. One seems justified in inferring from the above facts that the exciting cause of true status lymphaticus acts primarily on the thymus gland, commonly producing marked hyperplasia of this organ with an increase in or perversion of its internal secretion, and that this increased or perverted secretion is responsible for the general hyperplasia of lymphoid tissues, the lymphocytosis, and general feebleness of constitution which occur in this disease. This inference seems justified by the facts above noted, that the general hyperplasia of lymphoid structures, as well as all of the other symptoms of status lymphaticus, disappear when the *x*-rays reduce the thymus to normal size and, perhaps of more importance, to normal functional activity.

If the above hypothesis be true, that under pathological conditions an excess or perversion of the internal secretion of the thymns may produce hyperplasia of the thymus gland itself and of lymphoid tissues in general throughout the body, the inference seems plain that the normal thymus gland, which is at the height of its functional development in intra-uterine and early extra-uterine life, exercises a preponderating or controlling influence over the lymphoid tissues of the body, their functional capacity being increased or diminished by the increase or diminution of the internal secretion of the thymus. This hypothesis is in accord with the increased activity of lymphoid tissues during early life, and with the gradually diminishing activity of these tissues in later life, as the physiological atrophy of the thymus gland gradually diminishes its internal secretion.

The hypothesis that the thymus gland during infancy exercises an influence over the functions of lymphoid tissues explains many of the observations which have been made in connection with this gland.

Up to the present time, according to Warthin, seven cases of enlarged thymus producing thymic asthma have been cured by the partial or complete removal of the enlarged gland. One of these cases operated on by König was an infant only nine weeks old. Complete relief from the symptoms followed the operation, but König subsequently advised against complete thymectomy in these cases, because the patient operated on by him afterward developed rickets and did not walk until after it was four years of age. It will be noted that this case was operated upon at the very time in the life of the infant when the thymus gland is most active, and the infant was thereby deprived during the first and second year of its life of the physiological function of this organ, and thereby suffered profound nutritional disturbances.

The experiments of Basch, to the effect that extirpation of the thymus in "young" dogs is followed by lack of bony development and serious nutritional disturbances, is in accord with König's observations. Stokes, Ruhräh, Rohrer, Dudgeon, Bovaird, Nicholl, and many others have noted the fact that primary marasmus is associated with thymic atrophy. Warthin says that in primary marasmus thymic atrophy appears to be constant, and that similar changes also occur in the spleen and lymph glands, "suggesting a general lymphoid exhaustion." In these cases it would appear that the thymic atrophy is the initial lesion and one of the causative factors in the production of infantile marasmus. This condition would naturally occur if by destroying the functional activity of the thymus a "general lymphoid exhaustion," or general functional debility of all the lymphatic tissues resulted, in conformity with the hypothesis above outlined.

Warthin says that "in true acephalic monsters the thymus may be entirely absent, and up to the present time such cases are the only ones in which a total absence of the organ has been definitely shown to exist." These facts apparently indicate that there is some relationship between the absence of the thymus and the lack of development here referred to. If this be true, it points to the conclusion that the thymus gland during intra-uterine life exercises, by means of some internal secretion, a powerful influence over the metabolic processes which are necessary to the normal development of the fœtus. This conclusion is in accord with the hypothesis that the thymus gland exercises a controlling influence over the development and functional activity of lymphoid tissues.

Svehla[5] prepared fresh and dried thymus glands and fed them to dogs, with the following results: (1) Drop in blood pressure, as a result of weakness and paralysis of the vasoconstrictors. (2) Acceleration of the pulse due to the action of the toxin on the heart. (3) Large doses produced death of the animals, with restlessness, collapse, and dyspnœa, and postmortem examination showed death from suffocation.

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[5] Wien. med. Blatt., 1896.

Sachsa[6] injected a 10 per cent. watery solution into crural veins, and produced a fall in blood pressure, acceleration of the pulse, and death from acute suffocation. This toxic action was more marked in young animals. Both Svehla's and Sachsa's conclusions, that thymic asthma and thymic death may be due to hyperthymization of the blood, are in accord with my hypothesis.

On finishing this paper there came to my notice the research of Lucien and Parisot.[7] These observers made a careful study of the influence of thymectomy in rabbits, and found that in very young animals removal of the thymus was followed by a noticeable retardation of growth. The changes in the skeleton were in the weight and general dimensions of bones; no curvatures, epiphyseal enlargements, or bony softenings were found. The testicles and ovaries were diminished in size, corresponding with the lack of development of the organism in general. All of these changes were less noticeable in older animals, and did not occur at all in animals that had attained their full development. These findings of Lucien and Parisot may be explained by the hypothesis above advanced.

A CASE OF SPLENOMEGALY ASSOCIATED WITH MARKED ANEMIA OF THE PERNICIOUS TYPE.

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The following case seems worthy of being put on record, as it presents many unusual features. The patient has been under observation in London and Toronto during many years, and the history can thus be followed out in a way that is often not possible. The diagnosis offers many difficulties, but if, as seems probable, it be one of pernicious anemia, with a very large spleen, then in several ways it is a case of great rarity.

W. P., aged twenty-eight years and six months. Single. Lead glass worker. Admitted to the Toronto General Hospital on June 12, 1909.

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[6] Centralbl. f. allg. Path. u. path. Anat., 1897.

[7] Archiv. méd. exper. and d'anat. path., January, 1910.